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(54) Title: METHOD OF TREATMENT OF HEPATITIS			
(57) Abstract			
Hepatitis B is treated by administering an effective amount of 2',3'-dideoxyguanosine, 2',3'-dideoxyadenosine, or 2',3'-dideoxyinosine.			

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METHOD OF TREATMENT OF HEPATITISFIELD OF THE INVENTION

The present invention relates to a method for treating hepatitis B.

5 BACKGROUND OF THE INVENTION

Chronic infection with the hepatitis B virus (HBV) affects approximately 5% of the world's population. Chronic carriers of hepatitis B are at an increased risk of morbidity and mortality due to chronic liver disease, and a proportion of these will ultimately develop cirrhosis and/or hepatocellular carcinoma. At present, there is no therapy of proven benefit for chronic hepatitis B.

Although α -interferon has shown great promise in a subset of patients treated for prolonged periods of time, the response rates overall have, unfortunately, been disappointingly low.

The human hepatitis B virus is a member of a family of viruses known as hepadnaviruses. Other viruses in this family are the woodchuck hepatitis virus, the ground squirrel hepatitis virus, and the duck hepatitis B virus. These animal viruses have been invaluable models for characterization of hepadnaviruses and delineation of their unusual replicative cycle. These viruses replicate asymmetrically through an RNA template which requires reverse transcriptase activity, cf. Summers, Cell 29:403-415, 1982.

The 2', 3'-dideoxynucleosides are nucleosides which recently have been shown to have potent antiviral activity against the reverse transcriptase activity of the human immunodeficiency virus, HIV, as described by Mitsuya, et al. in Proc. Natl. Acad. Sci. USA 1986; 83:1911-1915. The most potent of these analogues is 2', 3'-dideoxycytidine, or DDC, which inhibits HIV in cell culture in concentrations as low as 10 nM, although 2', 3'-dideoxyadenosine (DDA) and 2', 3'-dideoxyguanosine (DDG), and 2', 3'-dideoxyinosine (DDI) are also potent inhibitors of HIV.

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It is an object of the present invention to overcome the above-mentioned deficiencies in the prior art.

It is another object of the present invention to provide methods for treating hepatitis B.

5 It is further object of the present invention to provide compositions for treating hepatitis B.

According to the present invention, hepatitis B can be treated by administering 2', 3'-dideoxyinosine (DDI), 2', 3'-dideoxyguanosine (DDG), or 2', 3'-
10 dideoxyadenosine (DDA) to a patient infected with hepatitis B. The 2', 3'-dideoxyinosine, 2', 3'-dideoxyguanosine, or 2', 3'-dideoxyadenosine, following anabolic phosphorylation, inhibits the reverse transcriptase of the hepatitis B virus.

15 While the exact mechanisms of the antiviral activity of the compositions according to the present invention are unknown, it is believed that the mechanism of action of DDA, DDG, or DDI is inhibition of viral polymerases, in particular, reverse transcriptases. DDA
20 DDG and DDI are nucleoside analogues, and they appear to prevent the formation of normal phosphodiester linkages once they become incorporated into a growing DNA chain. This process leads to "chain termination." DDI, and DDA
25 have a high affinity for reverse DDG, transcriptase, and, therefore, may inhibit replication of hepatitis B virus by preventing reverse transcription from the pregenomic RNA template. This interference in replication would lead to a decrease in serum levels of virus and a gradual fall in the amounts of hepatitis B virus DNA in the liver.

30 DDG, DDA and DDI are particularly attractive as antiviral agents because they are absorbed orally and has comparatively minimal side effects under the conditions used.

DETAILED DESCRIPTION OF THE INVENTION

35 2', 3'-dideoxyinosine, 2', 3'-dideoxyguanosine, or 2', 3'-dideoxyadenosine can be used for treating hepatitis B in patients so infected. The nucleosides are well absorbed orally, and are generally well tolerated.

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In vitro DDA triphosphate, DDG triphosphate, or DDI triphosphate have little effect on DNA polymerase activity of either duck hepatitis B virus or human hepatitis B virus. Previous researchers have used the in vitro assay to assess antiviral activity in hepatitis B cf. Nordenfelt, et al., Acta Path. Microbiol. Scand. Sect. B 87:75-76, 1979; and Hess, et al., Antimic. Agents Chemo. 19:44-50, 1981. However, it has now been discovered that this assessment may be unreliable as a means of screening antiviral agents. The DNA polymerase activity measured in serum from humans and ducks infected with hepadnaviruses may represent only one of the viral enzymes necessary for replication, and this activity may be relatively resistant to inhibition.

15 Serologic Assays

Serum DNA polymerase activity was determined by measuring ³H- thymidine incorporation into purified Dane particles by the method of Kaplan, et al., J. Virol. 12: 995-1005, 1973. The in vitro effects of DDI, DDA and DDG as a nucleotide analogues on DHBV and HBV were assessed using the DNA polymerase reaction. A range of concentrations of DDI, DDA or DDG triphosphate were incubated with purified Dane particles for one hour at 37°C, and the DNA polymerase reaction was then performed.

25 DHBV DNA was analyzed by molecular hybridization using a 3.0 kb, full-length DHBV DNA clone in CACYC184. The DHBV DNA insert was freed from plasmid A49 by digestion with EcoR1 and agarose gel electrophoresis. The DHBV DNA was radiolabelled with ³²P using the random primer method of 30 Feinberg, et al., ibid., to a specific activity of 3×10^7 to 1×10^8 cpm/ μ g.

DHBV DNA was detected in serum and liver tissue by slot blot analysis. For analysis of DHBV DNA in serum, 10 μ l of serum was denatured with 1 μ l of 1 M NaOH for five 35 minutes. The mixture was then neutralized by adding 90 μ l of 1 M ammonium acetate. For analysis of DHBV DNA in liver biopsy specimens, approximately 100 mg of minced liver was homogenized in 10 ml of ice cold 50 mM Tris, pH 8.5, 10 mM

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EDTA and 1% SDS. The crude liver homogenate was digested with proteinase K (200 µg/ml) for two hours at 50°C. Total cellular DNA was prepared by two extractions with a mixture of phenol and chloroform (1:1) in Tris pH 7.5. DNA was precipitated with absolute ethanol and diluted to a concentration of approximately 2 mg of DNA/ml in TE buffer.

One hundred microliters of the DNA sample prepared from serum or liver was spotted onto a nitrocellulose filter premoistened with 1 M ammonium acetate using a slot blot apparatus and vacuum manifold. The membrane was air dried and baked in a vacuum oven at 80°C for two hours and hybridized at 40°C with the DHBV DNA probe. The hybridized membranes were exposed to X-ray film for 5, 24, and 72 hours, and the resulting autoradiograms were scanned using Zenith Scanning Densitometer. The amount of DHBV DNA was quantified by comparing the autoradiographic signals for each sample with those of known amounts of cloned DHBV DNA dotted on the same filter diluted in normal serum or normal duck liver DNA.

Liver tissue DHBV DNA was also analyzed by Southern hybridization. Ten micrograms of total cellular DNA was subjected to horizontal slab gel electrophoresis in 1% agarose and transferred to nitrocellulose paper by the method of Southern, *J. Mol. Biol.* 98:503-517, 1975; as modified by Wahl, et al., *Proc. Natl. Acad. Sci. USA* 76: 3683-3687, 1979. Hybridization and autoradiography were carried out as described above.

STATISTICAL ANALYSES

Data were compared using Student's test, the Shapiro-Wilk test for normal distribution, and Spearman's rank correlation coefficient. Mean and standard deviations of serum DNA polymerase levels were calculated after logarithmic transformation of the data. Changes in serum and liver levels of these viral makers were expressed as percent inhibition of the pretreatment levels.

IN VIVO EFFECTS OF DDA ON DUCKS

CHRONICALLY INFECTED WITH DUCK HEPATITIS B VIRUS

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In contrast to the experience in vitro, DDA exhibited potent antiviral activity when given to ducks chronically infected with duck hepatitis B virus, for six days in doses similar to those used in human antiviral trials, cf. Yarchoan, et al., Lancet 1:76-81, 1988. The degrees of inhibition of both DNA polymerase activity and duck hepatitis B virus DNA were similar (67% and 69%, respectively) and were comparable to the degrees of inhibition of these markers reported in studies of other antiviral agents used in treatment of chronic hepatitis B. The antiviral effect was only partial, however, in that no duck became completely negative for duck hepatitis B virus DNA or DNA polymerase activity, and levels of these viral markers began to rise soon after the DDA therapy was stopped. These findings are similar to those reported with other antiviral agents used in chronic hepatitis B. A promising finding following DDA administration however, was that some inhibition of DNA polymerase activity and duck hepatitis B virus DNA was still observed for as long as twelve days after therapy was stopped. This observation is contrary to findings with adenine arabinoside and acyclovir, wherein following withdrawal of these agents, serum levels of duck hepatitis B virus often rebound to above pretreatment levels (Hirota, et al., Hepatology 7:24-28, 1987).

IN VIVO EFFECTS OF DDI AND DDG ON DUCKS

CHRONICALLY INFECTED WITH DUCK HEPATITIS B VIRUS

The effect of 2', 3'-dideoxyinosine and 2', 3'-dideoxyguanosine was assessed in eighteen Pekin ducks chronically infected with the duck hepatitis B virus (DHBV). Six ducks were given DDI and six ducks were given DDG at the rate of 0.8 mg/kg per injection by bolus every six hours for five days. The antiviral response was assessed by monitoring serum markers of viral replication, including DHBV DNA polymerase. The serum levels of DDI and DDG were 386 ng/ml and 772 ng/ml, respectively, at 20 minutes and 120 ng/ml and 50 ng/ml, respectively, at one hour after bolus injections.

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Antiviral therapy was tolerated well, and all ducks survived therapy and liver biopsy. No duck showed obvious evidence of drug toxicity.

TABLE

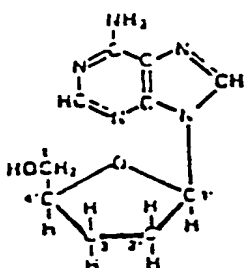
5 DHBV DNA Polymerase (cpm/0.2ml)

Group (no)	Day 1	Day 5	Day 18	
Control (6)	5107 ± 4009	5182 ± 4501	3571 ± 3070	
DDI	2417 ± 1609	1001 ± 850	630 ± 548	
10 DDG	3571 ± 3070	700 ± 229	1572 ± 412	

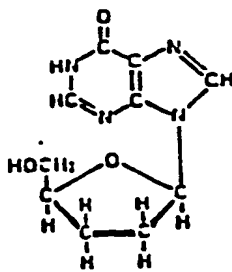
The TABLE shows that both DDG and DDI caused highly significant inhibition of DNA polymerase activity, 83% and 79%, respectively, by day 3 of treatment in all treated ducks as compared to the controls ($p < 0.01$). Both
 15 drugs caused a similar degree of inhibition. However, in 4 DDG treated ducks, a rebound in DNA polymerase activity was observed in the fifth day off of treatment. Rebound in DNA polymerase activity occurred in only one of six DDI treated ducks, and inhibition continued for up to thirteen
 20 days after stopping treatment and was significant compared to the control ($p < 0.01$) groups.

Treatment of two ducks with Ara-AMP yielded results similar to those reported by others, cf. Hirota, et al., op. cit. DNA polymerase and DHBV DNA levels decreased
 25 by 71% and 100% during therapy, but levels of these viral markers rapidly rose to greater than pretreatment values within four days of stopping the intramuscular injections.

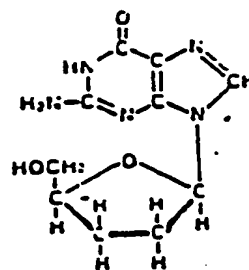
The nucleosides for use in the present invention have the following formulas:



dideoxyadenosine



dideoxyinosine



dideoxyguanosine

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The DDG, DDA, or DDI may be in the form of carboxylic acid esters in which the non-carbonyl moiety of the ester grouping is selected from straight or branched chain alkyl, alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy); sulfonate esters such as alkyl- or aralkyl-sulfonyl (e.g., methanesulfonyl); and mono-, di-, and triphosphate esters.

The compounds as described above also include pharmaceutically acceptable salts thereof. Unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group, including a substituted phenyl group.

Examples of pharmaceutically acceptable salts and pharmaceutically acceptable derivatives of the compounds which can be use in treating hepatitis B according to the present invention include base salts such as those derived from a base such as alkali metal (sodium, lithium, potassium), alkaline earth metal (magnesium) salts, ammonium and NX₄ where X is C₁₋₄ alkyl. Physiologically acceptable salts containing a hydrogen atom or any amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, maleic, isothionic, lactobionic, and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic, and p-toluenesulfonic acid, and inorganic acids such as hydrochloric, sulfuric, phosphoric, and sulfamic acids. Physiologically acceptable salts of a compound containing any hydroxy group include the anion of said compound in combination with a suitable cation such as Na⁺, NH₄⁺, and HX₄⁺ (wherein X is C₁₋₄ alkyl and X is halogen).

Specific examples of pharmaceutically acceptable derivatives of the compounds that may be used in accordance with the present invention include the monosodium salt and the following 5' esters: monophosphate, disodium monopho-

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sphate, diphosphate, triphosphate, acetate, 3-methyl butyrate, octanoate, palmitate, 3-chloro benzoate, 4-methyl benzoate, hydrogen succinate, pivalate, and methylate.

Also included within the scope of this invention
5 are the pharmaceutically acceptable salts, esters, salts of such esters, nitrile oxides, or any other covalently linked or non-linked compound which, upon administration to the recipient, is capable of providing, either directly or indirectly, a nucleoside analogue as described above, or an
10 antivirally active metabolite or residue thereof. All of these compounds are active and relatively nontoxic at concentrations of sufficient potency for effective inhibition of viral infectivity and replication.

It is possible for the nucleoside of the present
15 invention to be administered alone in solution. However, the active ingredient may be used or administered in a pharmaceutical formulation. These formulations comprise the nucleoside or derivative thereof together with one or more pharmaceutically acceptable carriers and/or other
20 therapeutic agents. As included within the scope of the present invention, "acceptable" is defined as being compatible with other ingredients of the formulation and not injurious to the patient or host cell.

The administration of DDG, DDA, or DDI to treat
25 hepatitis B can be accomplished by a variety of means of administration. Whatever administrative method is chosen should result in circulating levels of the nucleoside within a range of about 0.01 μM to about 2.0 μM . A range of approximately 0.05 to about 0.5 mg/kg administered every
30 four hours is considered to be a virustatic range in humans. In order to achieve this, the preliminary dosage range for oral administration may be broader, being, for example, 0.001-0.50 mg/kg administered every four hours. It is recognized that dosage modifications may be required
35 in individual patients to ameliorate or inhibit toxic side effects.

The pharmaceutical formulations according to the present invention may conveniently be administered in unit

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dosage form and may be prepared by any methods known in the pharmaceutical art. Determination of the effective amounts to be included in the dosage forms within the skill of the art.

5 The pharmaceutical compositions according to the present invention may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the DDA or DDI into preparations which can be used pharmaceutically. Preferably the
10 preparations, particularly those which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, an capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for admin-
15 istration by injection or orally, contain from about 0.1 to 99 percent, and preferably from about 25-85 percent, by weight, of DDC, together with the excipient.

 The pharmaceutical preparations of the present invention are manufactured in a manner which is itself
20 known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optically grinding a resulting mixture,
25 and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

 Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or
30 sorbitol, cellulose preparations and/or calcium phosphates, such as tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste using, for example, maize starch, wheat starch, rice starch, potato starch, and the like; gelatin, gum tragacanth, methyl cellulose,
35 hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and carboxymethyl starch, cross-linked polyvinyl

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pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate. Auxiliaries are, for example, flow-regulating agents and lubricants, such as silica, talc, stearic acid or salts thereof such as magnesium or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl-cellulose phthalate or hydroxypropylmethylcellulose phthalate are used. Dyestuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize different combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of combinations of the active ingredient with a suppository base. Suitable suppository bases include natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a

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base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, and paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds as appropriate oil injection suspensions may be administered. Suitable lypophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension such as sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

In the present invention, the hepatitis B may be treated by directly delivering the triphosphate derivative to the patient. It is well known that "unshielded" triphosphates cannot be used as drugs because triphosphate compounds do not penetrate cell membranes. Therefore, the triphosphate derivatives of this invention may be delivered by means of liposomes, small particles (about 25 μ M to about 1 μ M in diameter) which can serve as an intracellular transport system to deliver normally non-absorbable drugs across the cell membrane. Such use of liposomes for drug delivery is well known in the art, and is based upon the ability of a phospholipid to form bilayers spontaneously in aqueous environments.

One method of forming the liposomes is by agitating phospholipids in aqueous suspensions at high frequencies. This results in the formation of closed vesicles characteristic of liposomes. Once inside the cells, the triphosphate derivatives act to eliminate the replication of the hepatitis B virus. Since the triphosphate has been shown to be active inside the cells, and to be the active form therein, the liposome is clearly a method of choice for delivery of these drugs.

Formulations suitable for vaginal administration may be in the form of pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing, in addi-

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tion to the active ingredient, such carriers as are known in the art to be appropriate.

The formulations according to the present invention may be in unit-dose or multi-dose sealed containers, such as ampoules and vials, and may be stored in a lyophilized condition requiring only the addition of the sterile liquid carrier for injections immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

In treating hepatitis B according to the present invention, the medication is generally administered two to six times a day. In order to improve oral bioavailability, it is often preferable to add a common buffer such as sodium acetate to a solution containing a nucleoside according to the present invention.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation.

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WHAT IS CLAIMED IS:

1. A method for treating hepatitis B comprising administering to a patient infected with hepatitis B an effective amount of a nucleoside selected from the group consisting of 2', 3'-dideoxyinosine and 2', 3'-dideoxyadenosine, and 2', 3'-dideoxyguanosine.
2. The method according to claim 1 wherein the nucleoside is in the form of a triphosphate salt.
3. The method according to claim 1 wherein the nucleoside is in a pharmaceutically acceptable carrier.
4. The method according to claim 3 wherein the carrier is normal saline.
5. The method according to claim 2 wherein carrier is a liposome.
6. The method according to claim 1 wherein the nucleoside is administered in a dosage range of from about 0.03 to about 0.5 mg/kg administered from two to twelve times daily.
7. The method according to claim 1 wherein the nucleoside is administered orally.
8. The method according to claim 1 wherein the nucleoside is administered intravenously.
9. The method according to claim 1 wherein the nucleoside is administered intramuscularly.
10. The method according to claim 1 wherein the nucleoside is administered rectally.
11. The method according to claim 1 wherein the nucleoside is in the form of a lyophilized powder and is administered intranasally.
12. The method according to claim 1 wherein the nucleoside is 2', 3'-dideoxyadenosine.
13. The method according to claim 1 wherein the nucleoside is 2', 3'-dideoxyinosine.
14. The method according to claim 1 wherein the nucleoside is 2', 3'-dideoxyguanosine.
15. A composition comprising a nucleoside selected from the group consisting of 2', 3'-dideoxyino-

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sine, 2', 3'-dideoxyadenosine and 2', 3'-dideoxyguanosine, in a pharmaceutically acceptable carrier.

16. The composition of claim 15 wherein the nucleoside is in the form of a triphosphate salt.

5 17. The use of a nucleoside selected from the group consisting of 2', 3'-dideoxyinosine, 2', 3'-dideoxyadenosine, and 2', 3'-dideoxyguanosine for the treatment of hepatitis B infection.

10 18. The use according to claim 17, wherein the nucleoside is in the form of a triphosphate salt.

19. The use according to claim 17, wherein the nucleoside in a pharmaceutically acceptable carrier.

20. The use according to claim 19, wherein the carrier is normal saline.

15 21. The use according to claim 20, wherein the carrier is a liposome.

22. The use according to claim 17, wherein the nucleoside is given in a dosage of from about 0.03 to about 0.5 mg/kg administered two to twelve times daily.

20 23. The use according to claim 17 wherein the nucleoside is administered orally.

24. The use according to claim 17 wherein the nucleoside is administered intravenously.

25 25. The use according to claim 17 wherein the nucleoside is administered intramuscularly.

26. The use according to claim 17 wherein the nucleoside is administered rectally.

30 27. The use according to claim 17 wherein the nucleoside is in the form of a lyophilized powder and is administered intranasally.

28. The use according to claim 17 wherein the nucleoside is 2', 3'-dideoxyadenosine.

29. The use according to claim 17 wherein the nucleoside is 2', 3'-dideoxyinosine.

35 30. The use according to claim 17 wherein the nucleoside is 2', 3'-dideoxyguanosine.

INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US90/02686**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 31/70 U.S. CL: 514/45, 46, 47, 48, 894						
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched ⁴</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 50%; text-align: left; border-bottom: 1px solid black;">Classification System</th> <th style="width: 50%; text-align: left; border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">U.S. CL.</td> <td style="padding: 5px;">514/45, 46, 47, 48, 894</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵</div>			Classification System	Classification Symbols	U.S. CL.	514/45, 46, 47, 48, 894
Classification System	Classification Symbols					
U.S. CL.	514/45, 46, 47, 48, 894					
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴						
Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸				
X	EP, A, 0,206,497 (KOSZALKA ET AL.) 30 December 1986, see pages 3,5,10-15 and the claims.	1-30				
X Y	US, A, 4,704,357 (MITSUYA, ET AL.) 03 November 1987, see figs 1-4 and examples.	15 16				
Y	Proceeding of the National Academy of Science, volume 83, March 1986, H. MITSUYA, ET AL., "Inhibition of the <u>in vitro</u> Infectivity and Cytopathic Effect of Human T-Lymphotropic Virus Type III/Lymphadenopathy-associated Virus (HTLV-III/LAV) By 2', 3'-dideoxy-nucleosides", see pages 1911 or 1912.	1-30				
A	The Lancet, volume 1, 16 January 1988, R. YARCHOAN, ET AL; "Phase I Studies of 2', 3'-Dideoxycytidine in severe Human Immunodeficiency Virus Infection as a single agent and alternating, with Zidovudine (AZT)" see page 76.	1-30				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search ² 08 AUGUST 1990	Date of Mailing of this International Search Report ³ <div style="text-align: center; font-size: 1.2em; font-weight: bold;">4 OCT 1990</div>					
International Searching Authority ¹ <div style="text-align: center;">ISA/US</div>	Signature of Authorized Official ¹⁹ <div style="display: flex; justify-content: space-between; align-items: center;"> <div style="text-align: center;"> JOHN W. ROLLINS </div> <div style="text-align: center;"> NGUYEN NGOC-HO INTERNATIONAL DIVISION </div> </div>					

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